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Gram-Scale Laboratory Synthesis of TC AC 28, a High-Affinity BET Bromodomain Ligand

Raysa Khan,[†] Graham Marsh,[§] Robert Felix,[§] Paul D. Kemmitt,[‡] Matthias G. J. Baud,[∥,⊥] Alessio Ciulli,[∥] and John Spencer*[,†]

[†]Department of Chemistry, School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, U.K.

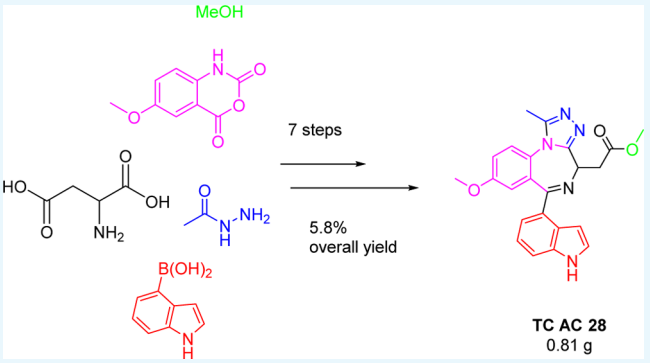
[‡]Oncology, AstraZeneca, 310 Cambridge Science Park, Milton Road, Cambridge CB4 0WG, U.K.

[§]Tocris Bioscience, the Watkins Building, Atlantic Road, Avonmouth, Bristol BS11 9QD, U.K.

[∥]Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, James Black Centre, Dow Street, Dundee DD1 5EH, U.K.

Supporting Information

ABSTRACT: **TC AC 28**, 6-(1*H*-Indol-4-yl)-8-methoxy-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-4-acetic acid methyl ester, has been synthesized on a near-gram scale in seven steps with notable improvements in the reported poor-yielding last two steps enabling this key chemical probe compound to be available for researchers.



INTRODUCTION

The 1,4-benzodiazepine scaffold is a well-established "privileged scaffold" in medicinal chemistry,[1−16] and we have an active interest in synthesizing libraries of such compounds.[17−21] Our recently described triazolo-benzodiazepine derivative **TC AC 28** is a potent, selective bromo and extraterminal bromodomain inhibitor and a useful epigenetic tool compound, with a crystallographically defined binding mode to the target protein and displaying K_d values of 40 and 800 nM toward Brd2(2) and Brd2(1), respectively.[22,23] We sought to scale up the original seven-step-protocol toward the racemic product (as in the original manuscript) with the aim of improving the final two problematic and low-yielding steps.[23]

RESULTS AND DISCUSSION

Our scale-up efforts (step 1, Scheme 1) started with a synthesis of the methyl ester hydrochloride salt **2**, which was formed in virtually quantitative yield, followed by a cyclization step (step 2) to afford the isatoic anhydride **4**.[24]

Reaction of the latter formed the benzodiazepinedione **5**, and we employed an ether trituration, as opposed to our earlier reported chromatographic purification workup. This was followed by treatment with Lawesson's reagent[25,26] and then mercury-mediated cyclization to afford the triazolo-analogue **7** (steps 3−5). At this stage, no significant differences in yields were noticed from our original report and we did not attempt less toxic routes to **7** given that the yield was acceptable and the chemistry scalable. However, the next two crucial steps were vital in our aims to obtain approximate gram quantities of product.

Step 6 (Scheme 2) was originally performed by combining 12 batches of ca. 170 mg of precursor **7**, producing the key chloroimidate intermediate **8**, which was obtained as a white solid in 29% yield (619 mg). Careful reexamination of this step led us to significantly lower the amounts of $POCl_3$ used, and we were able to avoid the inefficient chromatographic step by carrying out a trituration in Et_2O (Table 1, entry 3). Indeed, we were delighted to obtain a yield of 76% of **8** in near-gram quantities (0.80 g) in a one-step protocol.

Buoyed by this result, we next examined the final Pd-catalyzed Suzuki−Miyaura coupling reaction to install the indolyl group in **9**.[27,28] Maintaining the original $Pd(PPh_3)_4$ catalyst, we obtained, by using a 1,2-dimethoxyethane (DME)/water mixture with Na_2CO_3 as base, **9** in 49% yield (Table 3, entry 2), which was scalable to 0.8 g of product (Table 2).

CONCLUSIONS

Overall, acceptable, near-gram quantities of the final product **9** have been synthesized, benefitting ultimately from improved steps **6** and **7** of the original synthetic route (Table 3).

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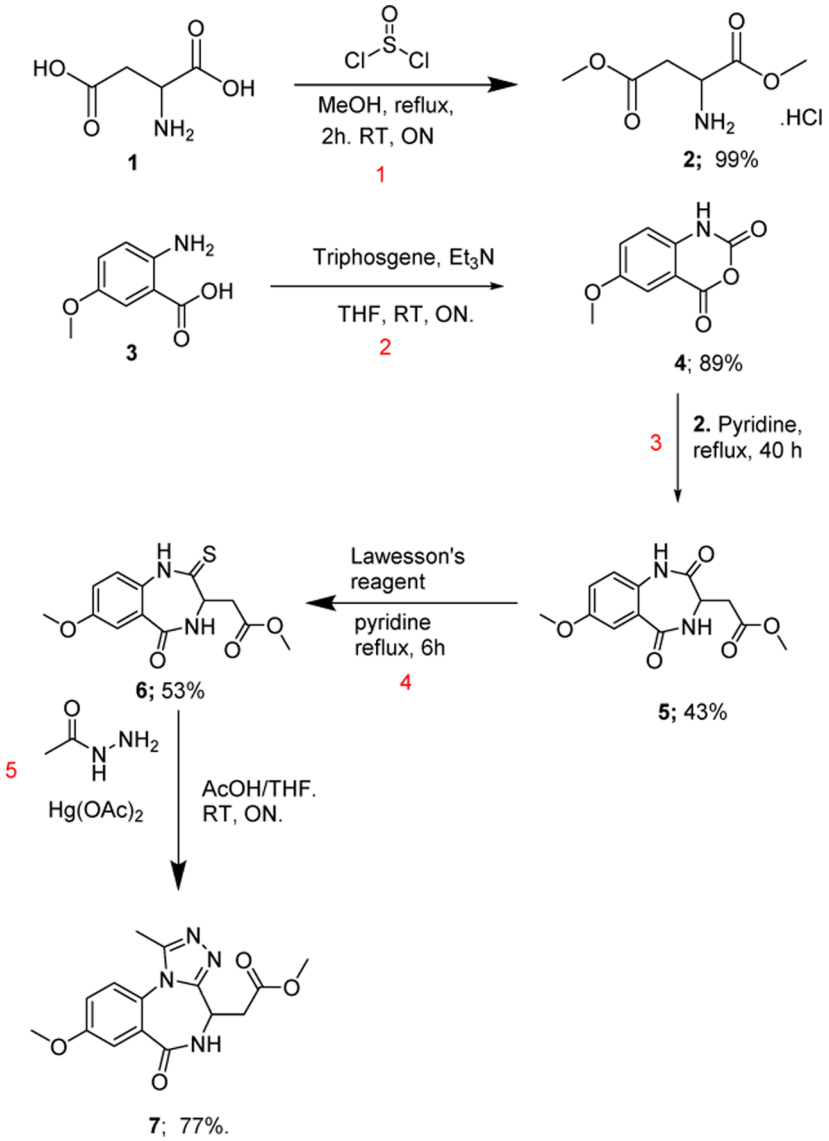
Scheme 1. Synthesis of Triazolo-Benzodiazepinone, 7



EXPERIMENTAL SECTION

All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer and prepared in deuterated solvents, such as $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6. Liquid chromatography mass spectra (LCMS) were acquired using an Agilent 6120 (600 bar) HPLC with Agilent 1290 MCT column compartment oven and Agilent 6120 Quad Mass spectrometer, and percentage purities were run on a Zorbax SB C18 2.1 × 50 mm^2 1.8 μm column (0.1% aq formic acid, 0.1% formic acid in MeCN 5−95%, 0.1% trifluoroacetyl (TFA)/MeCN, over 5 min, held at 100% for 2 min; flow rate, 0.5 mL/min) with UV detector at 250 nm and bandwidth 100 nm. Purifications were performed by flash chromatography on silica gel columns using a Reveleris PREP purification system.

(DL)-Aspartic Acid Dimethyl Ester Hydrochloride (2). To a suspension of DL-aspartic acid (50.00 g, 375.65 mmol) in methanol (300 mL) at 0 °C, thionyl chloride (68.50 mL, 939.14 mmol, 2.5 equiv) was dropwise added at such a rate that the temperature was maintained below 10 °C. Upon completion of the addition, the reaction mixture was stirred at reflux for 2 h and then allowed to cool to ambient temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure, and the resulting viscous oil was triturated from diethyl ether, filtered, and dried at 40 °C under vacuum, affording the product as a white solid (74.00 g, >99%). The spectral data were consistent with those reported.[29]

5-Methoxyisatoic Anhydride (4). To a stirred solution of 2-amino-5-methoxy-benzoic acid **3** (15.00 g, 99.23 mmol) and triethylamine (13.80 mL, 99.23 mmol, 1 equiv) in tetrahydrofuran (THF) (500 mL) at 0 °C, triphosgene (29.45 g, 99.23 mmol, 1 equiv) was portionwise added at such a rate that the temperature was maintained below 5 °C. Upon completion of the addition, the reaction mixture was stirred for 18 h at ambient temperature. The reaction was recooled to 0 °C, and H_2O (15 mL) was added in a dropwise fashion at such a rate that the temperature was maintained below 10 °C. After stirring for a further 30 min at ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was triturated with H_2O, and the resulting solid was collected

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Scheme 2. Synthesis of TC AC 28 (9)

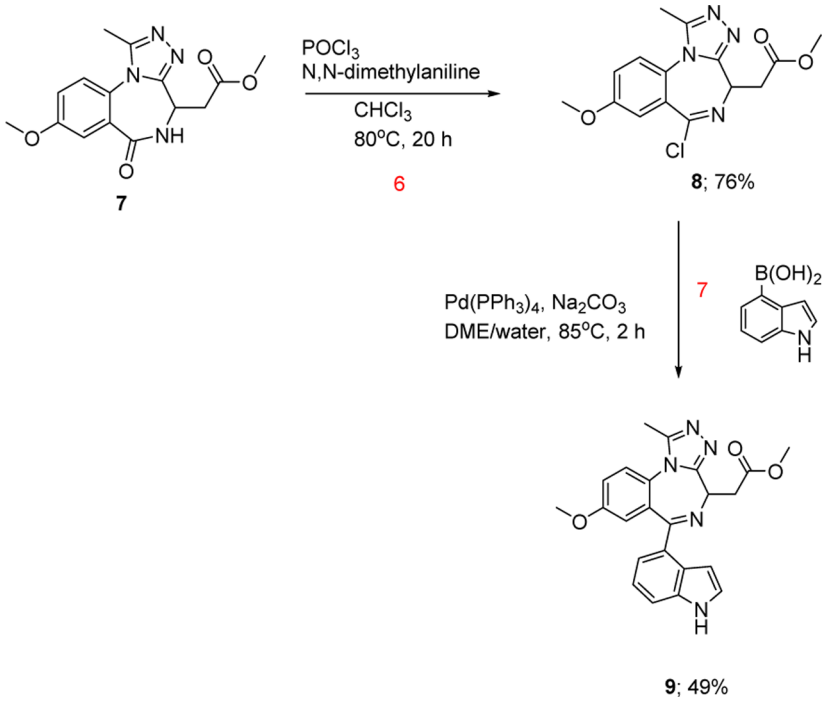

Table 1. Step 6 Optimization

entry	$POCl_3$ (equiv)	dimethylaniline (*N*,*N*-DMA) (equiv)	workup	purification	isolated yield (**8**) (%)
1	21	5.5	quench (Et_3N)	acetone/DCM (30−80%) column	20[a]
2	10	3	quench (water) extraction with $CHCl_3$	trituration with diethyl ether	50
3	1.5	2	quench (water) extraction with $CHCl_3$	trituration with diethyl ether	76

[a]Material decomposes on silica.

Table 2. Suzuki Coupling Optimization

entry	catalyst	solvent	base	conditions	isolated yield (**9**) (%)
1	$Pd(PPh_3)_4$	dimethylformamide	Et_3N	100 °C, 24 h	27
2	$Pd(PPh_3)_4$	DME/water	Na_2CO_3	85 °C, 2 h	49

Table 3. Comparison of Scale-Up vs Original Published Route

step	S.M. (g)[a]	prod. (g)	yield (%)	S.M. (g)[b]	prod. (g)	yield (%)
1	50.07	74.00	>99			
2	50.02	57.03	89			>99
3	45.00	27.30	43[c]	3.70	1.77	36
4	15.01	8.30	53	1.86	1.12	57
5	8.00	6.57	77[d]	2.20	2.15	91
6	0.99	0.80	76[e]	2.04 (0.17 × 12)	0.619	29
7	1.33	0.81	49			27−31

[a]Scale-up (this work); S.M. = starting material, prod. = product. [b]Original papers. [c]Trituration in ether as opposed to chromatography. [d]Reaction mixture quenched with $NaHCO_3$, extracted with ethyl acetate as opposed to no workup. [e]$POCl_3$ (1.5 equiv), DMA (2 equiv) quenched with water, extraction with $CHCl_3$, and trituration with diethyl ether as opposed to $POCl_3$ (21 equiv). DMA (5.5 equiv), quenched with Et_3N and purified by chromatography.

by filtration and dried at 50 °C under vacuum, affording the product as a brown solid (17.00 g, 89%). LCMS purity (UV): 99%, t_R 3.24 min. The NMR data were consistent with those reported.[23]

Methyl-2-(7-methoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetate (5). 5-Methoxyisatoic anhydride **4** (45.00 g, 232.97 mmol) and DL-aspartic acid dimethyl ester hydrochloride (46.04 g, 232.99 mmol, 1 equiv) were suspended in pyridine (600 mL), and the reaction mixture was stirred at reflux for 18 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 mL) and 2 M HCl (500 mL). The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (2 × 350 mL). Some solid material at the phase boundary was collected by filtration, giving an initial crop of product. The combined organic phase of the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. Trituration with diethyl ether afforded the product as a white solid (27.30 g, 43%). LCMS purity (UV): 96%, t_R 3.12 min. The NMR data were consistent with those reported.[23]

(+/−)-Methyl-2-(7-methoxy-5-oxo-2-thioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetate (6). To a suspension of the previous compound **5** (15.01 g, 53.91

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mmol) in pyridine (265 mL), Lawesson's reagent (19.62 g, 48.52 mmol, 0.9 equiv) was added, and the reaction mixture was stirred at reflux for 6 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was suspended in CH_2Cl_2 (3 × 300 mL) and reconcentrated under reduced pressure. Trituration with CH_2Cl_2 afforded the product as a pale yellow solid (8.30 g, 53%). LCMS purity (UV): 92%, t_R 3.51 min. The NMR data were consistent with those reported.[23]

(+/−)-Methyl-2-(8-methoxy-1-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-acetate (7). To a stirred suspension of compound **6** (8.00 g, 27.18 mmol) and acethydrazide (6.04 g, 81.53 mmol, 3 equiv) in THF (120 mL), acetic acid (80 mL) was added. The reaction mixture was cooled to 0 °C, and mercury (II) acetate (12.91 g, 40.77 mmol, 1.5 equiv) was added to the reaction mixture portionwise at such a rate that the temperature was maintained below 5 °C. Upon completion of the addition, the reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to ambient temperature and stirred for 48 h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between $NaHCO_3$ (sat. aq., 450 mL) and ethyl acetate (300 mL). The aqueous component was separated and extracted with ethyl acetate (2 × 300 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was collected as a white solid (6.57 g, 77%) after flash column chromatography (95:5 CH_2Cl_2/MeOH). LCMS purity (UV): 95%, t_R 3.15 min. The NMR data were consistent with those reported.[23]

(+/−)-Methyl-2-(6-chloro-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetate (8). To a solution of compound **7** (0.99 g, 3.13 mmol) in $CHCl_3$ (20 mL), *N*,*N*-dimethylaniline (0.79 g, 6.26 mmol) and $POCl_3$ (0.72 g, 4.70 mmol) were added under inert atmosphere, and the reaction was heated at 80 °C for 18 h. After cooling to room temperature, the reaction was slowly poured into lukewarm water (80 mL) with stirring. After stirring for 15 min, it was diluted with $CHCl_3$ (50 mL) and the layers were separated. The aqueous layer was extracted with further $CHCl_3$ (50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with diethyl ether to afford an off-white solid (0.80 g, 76%). The product was used without further purification. LCMS purity (UV): 97%, t_R 3.94 min. The NMR data were consistent with those reported.[23]

(+/−)-Methyl-2-(6-chloro-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetate (9). To a stirred suspension of compound **8** (1.33 g, 3.97 mmol) in DME (14 mL), a solution of Na_2CO_3 (0.76 g, 7.17 mmol) in water (6 mL) was added, followed by the addition of indole-4-boronic acid (0.77 g, 4.76 mmol) and $Pd(PPh_3)_4$ (0.31 g, 0.27 mmol), and the reaction was heated at 85 °C for 2.5 h. After cooling to ambient temperature, it was filtered over celite, and the filtrate was partitioned between EtOAc/water. The layers were separated, and the organic layer was further washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was collected as a white solid (0.81 g, 49%) after flash column chromatography (rf = 0.35; 95:5 CH_2Cl_2/MeOH). ^{1}H NMR (400 MHz) $CDCl_3$: δ = 8.40 (s, 1H), 7.52 (d, J = 8.0, 1H), 7.42 (d, J = 9.0, 1H), 7.24 (t, J = 3.0, 1H), 7.20 (dd, J = 3.0, J = 9.0, 1H), 7.15 (t, J = 7.5, 1H), 7.08 (d, J = 7.5, 1H), 6.92 (d, J = 3.0, 1H), 6.58 (s, 1H), 4.78 (dd, J = 5.5, J = 9.0, 1H), 3.81 (s, 3H), 3.72−3.78 (m, 4H), 3.63 (dd, J = 5.5, J = 16.5, 1H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.5, 168.1, 157.9, 156.4, 150.5, 136.5, 131.9, 130.8, 126.9, 126.4, 125.5, 124.3, 123.4, 121.2, 117.7, 116.5, 113.6, 103.1, 55.8, 53.4, 51.9, 36.9, 12.2. LCMS purity (UV): 99%, t_R 4.12 min. Elemental analysis: calcd for $C_{23}H_{21}N_5O_3.^{3/4}H_2O$ (%): C, 64.40, H, 5.29, N, 16.33, found: C, 64.73, H, 5.12, N, 16.07. MS m/z (ES+) calculated for $C_{23}H_{21}N_5O_3$ $[+H]^+$: 416.3 found: 416.3; m/z (ES−) calcd for $C_{23}H_{21}N_5O_3$ $[-H]^+$: 414.3 found: 414.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00780.

Scanned NMR spectra and HPLC purity for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.spencer@sussex.ac.uk.

ORCID

Matthias G. J. Baud: 0000-0003-3714-4350

Alessio Ciulli: 0000-0002-8654-1670

John Spencer: 0000-0001-5231-8836

Present Address

$^{\perp}$Chemistry Department, Faculty of Natural and Environmental Sciences, University of Southampton, Southampton SO17 1BJ, U.K. (M.G.J.B.).

Author Contributions

All authors have given approval to the final version of the manuscript.

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Notes

The authors declare the following competing financial interest(s): the title product, **TC AC 28**, is sold under license from the University of Dundee and is available at Tocris on: https://www.tocris.com/dispprod.php?ItemId=519094#.WShYEU3rvIU.

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■ ABBREVIATIONS

TLC, thin-layer chromatography; *N*,*N*-DMA, dimethylaniline

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